

Neonatal fungal infections: new strategies in diagnosis

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Proceedings

Proceedings of the 10th International Workshop on Neonatology · Cagliari (Italy) · October 22nd-25th, 2014

The last ten years, the next ten years in Neonatology

Guest Editors: Vassilios Fanos, Michele Mussap, Gavino Faa, Apostolos Papageorgiou

Abstract

In Neonatal Intensive Care Unit, fungal sepsis are the third leading cause of late onset sepsis among very low birth weight neonates. Many of biomarkers known are neither sensitive nor specific enough to provide an accurate diagnosis of invasive fungal infections. Indeed even today, the “gold standard” in the diagnosis of neonatal fungal sepsis is positive blood culture. Since neonatal sepsis is a multiorgan disorder that leads to metabolic changes in the organism, new technologies such as metabolomics are becoming a promising method in early diagnosis and are capable of predicting onsets, thus allowing personalized treatment and monitoring of neonatal sepsis.

Keywords

Fungal infections, newborn, sepsis, metabolomics.

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How to cite

Dessì A. Neonatal fungal infections: new strategies in diagnosis. J Pediatr Neonat Individual Med. 2014;3(2):e030222. doi: 10.7363/030222.

Introduction

Fungal infections are an important cause of mortality and morbidity in the neonatal period, especially in preterm infants. Most cases of neonatal fungal sepsis are caused by *Candida spp.*, rarely by other yeasts (such as *Aspergillus spp.*, etc.). The *Candida spp.* are commensal organisms that colonize the skin, mucose surfaces and are also capable of adhering to catheter surfaces. Owing to the immaturity of the neonate's immune system, which hinders the development of the defenses of skin and mucous membranes, *Candida spp.* can invade the blood flow and spread, thus making it difficult to eradicate such infections [1]. Moreover, as in the baby, also in the neonate fungal colonization is the most important risk factor in the progression to systemic fungal infection. Neonatal fungal sepsis is normally "late", that is, the infection has an onset after more than 72 hours from birth and is prevalently by nosocomial transmission. The diagnosis is often difficult since the neonate may present a slight symptomatology with an onset that cannot always be identified. A blood culture is essential for the diagnosis, but may not be the gold standard in neonatology, since it often produces a negative result due to technical difficulties connected with its timing and problems in obtaining suitable amounts of blood [2]. Neonatal fungal infections are characterized by an extremely high mortality rate: in the several observational studies it has been estimated at between 25% and 60% of infected neonates and depends dramatically on the timeliness of the diagnosis and consequent treatment [3].

Clinical diagnosis

Candida spp. are ubiquitous yeasts; they are physiologically present in healthy individuals, their main reservoir being the digestive tract. Other sites, such as the oropharynx, the vagina, the lower respiratory and urinary tracts can also be colonized. In most cases *Candida* infections are paucisymptomatic and only rarely lead to invasive candidosis [4]. This occurs when the *Candida spp.* enter the blood circulation, thus causing candidemia and systemic diffusion. This is in fact an opportunistic infection that presents only in individuals affected by pathological conditions that determine a reduced or altered level of defences or because of the disease itself or the therapy applied. The *Candida spp.* involved in the pathogenesis of

cases of invasive candidosis are changing, with an increase in *non albicans Candida* species which are also more resistant. In the latter case, candidosis represents a typical nosocomial infection. In the first weeks of life of neonates and preterms the *Candida spp.* are to be considered pathogenous germs owing to not yet completely developed cell immunity. This fungus is capable of rapidly colonizing the skin and mucous membranes of some 60% of neonates in serious conditions; from colonization to invasion in these patients the step is short. Fungal infections cover 9% of cases of late onset sepsis of infants weighing less than 1,500 grams: they are associated with a mortality of 7% among infants in whom the infection does not develop [3].

Old strategies in diagnosis

It is quite difficult to arrive at a definite diagnosis of systemic fungal infections in neonates in consideration of the aspecificity of the symptomatology and the limited efficacy of laboratory tests. Moreover, the blood culture, which is supposedly the gold standard in isolating the causal agent, varies in sensitivity (between 25% and 80% in the preterm neonate) and what is more, in neonates it is not always easy to perform it correctly and at the proper time. *Candida spp.* grow in blood cultures and in those of blood-agar; however, if infections by other fungi are suspected recourse to other special cultures is necessary. Blood cultures for the identification of fungi may require from 4 to 5 days of incubation before becoming positive and may result negative even in manifestly disseminated diseases [5]. Besides the isolation of fungi from blood, other biomarkers are used in clinical practice (for example circulating antigens) which have been studied with different specificities and sensitivities, but none appear to play a significant role in the diagnosis of fungal infections in neonatal patients [6].

New strategies in diagnosis

Fungal sepsis are one of the major problems in neonatal and pediatric intensive therapy units. The availability of new diagnostic techniques may lead pediatricians to rapid identification of septic patients and improve their outcome. Recently, single biomarkers that appear to be useful in routine clinical practice have been identified (**Tab. 1**). The study by Montagna et al. [7] suggests

Table 1. New biomarkers useful in diagnosing neonatal fungal sepsis.

Marker	Studies
1→3-β-d-glucan	Montagna et al., 2011 [7] Goudjil et al., 2013 [8]
Combined CRP and IL-6	Oguz et al., 2011 [9]
Presepsin	Mussap et al., 2011 [10]

that a regular monitoring of serum circulating antigens (i.e., 1→3-β-d-glucan), combined with other microbiological and clinical information, may provide earlier and more accurate diagnoses in neonatal and pediatric patients with candidemia. The results of this study have recently been confirmed in a work performed by Goudjil et al. [8] where the levels of 1→3-β-d-glucan were found to be higher in invasive *Candida spp.* neonatal infections. Variations in the serum levels of this biomarker may also be useful in assessing the effectiveness of the antifungal therapy. A study by Oguz et al. [9] examined the predictive value of the combined evaluation of the C-reactive protein (CRP) and interleukin-6 (IL-6) responses for differentiating fungal and bacterial aetiologies in patients with neonatal sepsis. The authors conclude that the combined evaluation of the CRP and IL-6 responses better predicted the causative micro-organism in neonatal infections. In recent literature presepsin is emerging as a new marker of sepsis. The clinical utility of this new biomarker in separating bacterial infections from those that are not (including the systemic inflammatory response syndrome) has been studied and compared to procalcitonin and IL-6 in a multicentric prospective study on adult patients [11]. Presepsin was found to be useful in the diagnosis of bacterial and fungal sepsis and showed better sensitivity compared to conventional markers and blood culture. Presepsin has been found to be a reliable marker also in the field of neonatal infections, specifically for very early diagnosis, classification into class of severity, and prediction of complications and death [10]. A recent study shows that the technique of microsatellites can be useful in detecting the presence of an outbreak of *C. parapsilosis* in the NICU, thus emphasizing the importance of using molecular tools for early detection of hospital outbreaks and introduction of effective preventive measures, especially in such units [12]. However, despite the many and extended investigations that have been performed in the latest decades on the biochemical

parameters of sepsis, there is still no single test that satisfies the criteria for being the ideal marker in the early diagnosis of neonatal sepsis. Since neonatal sepsis is a complex disorder involving different organs that leads to wide variations in the organism's metabolites, metabolomic analyses appear to be a promising method owing to their high sensitivity and specificity in determining metabolic variations correlated with sepsis [13]. In fact, analysis of the metabolic profile in a body fluid provides the immediate identification of changes in the composition of endogenous and exogenous metabolites that may be correlated with specific pathophysiological states, gene expression and interaction with the environment. Up to now, few publications have dealt with the contribution of metabolomics in revealing sepsis in adults and children [13, 14]. In a quite recent original paper by Fanos et al. [15], metabolomic techniques are employed to assess variations in metabolites preceding the development of early and late onset sepsis in neonates. This study identified the metabolites responsible for the differences between septic neonates and controls, already at birth for early onset sepsis and within 72 hours before its clinical appearance for late onset sepsis. The data emerging from this study suggest that with the application of metabolomics in the very near future it will be possible to perform the dosage of sensitive and specific metabolites of sepsis so as to begin more targeted treatments, also in the case of neonatal fungal infections. Similarly, an example of how neonatal fungal infections in single patients could be monitored with metabolomics is presented by the same authors [16].

Conclusions

Considering the frequency of neonatal fungal infections, their careful management (diagnosis and treatment) is common practice in neonatal intensive care. Candidosis is therefore an important clinical issue in caring for hospitalized and immunocompromised infants. To reduce the incidence and mortality connected with pathologies caused by *Candida spp.*, in particular invasive candidosis, it is of fundamental importance to follow an approach that takes into account the epidemiological picture and is based on an early, sensitive and specific diagnosis. Present-day methods and procedures for the diagnosis of neonatal fungal infections are hindered by low sensitivity and long response times. They

cannot meet the need to proceed to a rapid and efficacious therapeutic treatment. In this field, certain new biomarkers appear to be effective. In particular, metabolomic analyses are becoming a most promising method since they make an early diagnosis possible and are capable of predicting onsets, thus allowing personalized treatment and monitoring of neonatal sepsis.

Declaration of interest

The Author declares that there is no conflict of interest.

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